Childhood Cancer Survivor Study(CCSS)
U24 CA055727

Principal Investigator: Greg Armstrong, MD, MSCE

NIH NATIONAL CANCER INSTITUTE

June 15, 2020
Nita Seibel, MD
Scientific Liaison
William Timmer, PhD
Program Director

Childhood Cancer Survivor Study (CCSS) Background (U24 CA55727)

- Retrospectively ascertained cohort with ongoing, longitudinal follow-up of survivors of pediatric and adolescent cancer diagnosed between 1970-1999; < 21 years old, English or Spanish speaking; Leukemia, lymphoma, CNS, Wilms, NBL, soft-tissue and bone sarcoma
- 37,593 eligible 5- year survivors (evaluable for late mortality studies); 25,664 participants;14,361 (diagnosed 1970-86); 11,303 (1987-99); 5059 sibling controls
- Data collection: detailed treatment including RT organ-based dosimetry; Biospecimens - germline DNA; SMN somatic tissue; ***Open resource***
- Self-reported health/psychosocial outcomes and risk factors collected at baseline and on six longitudinal follow-up surveys
- 367 Publications >700 Investigators, 80 trainees
- 54 Investigator-initiated studies; $53.1 million grant support;

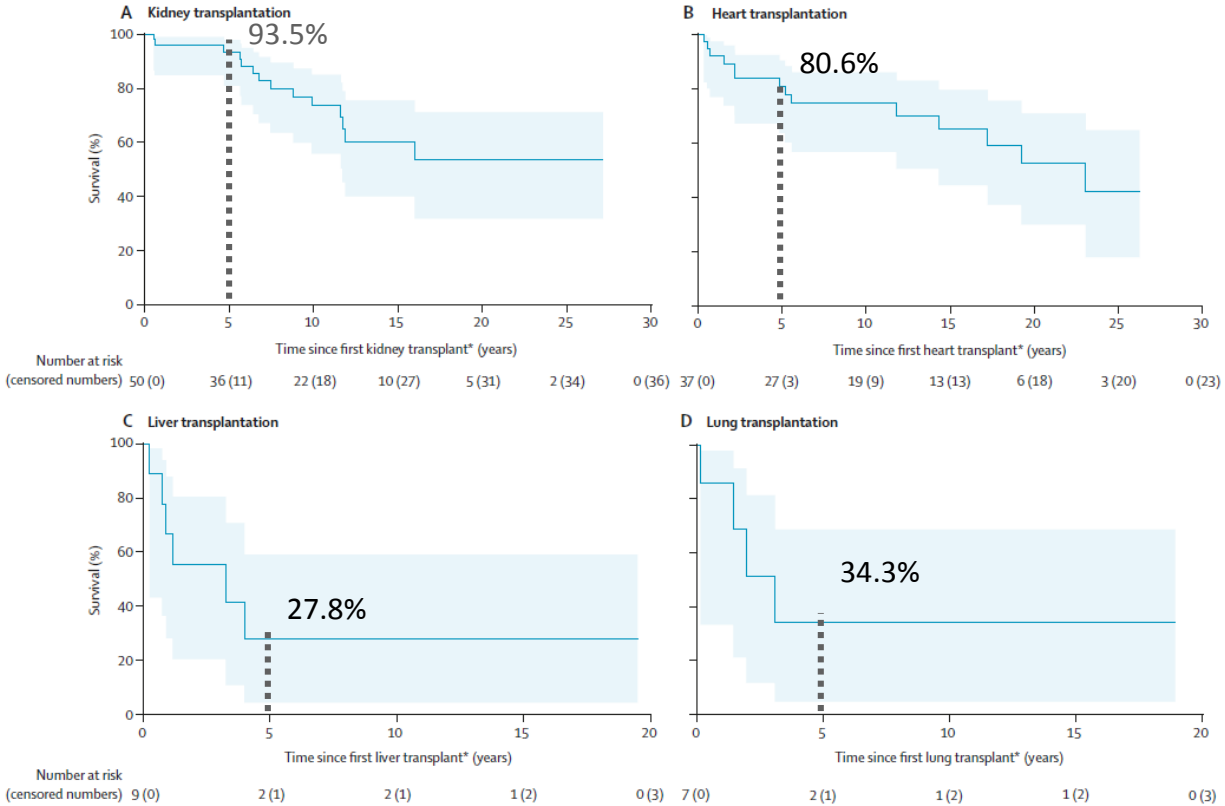
CCSS Impact on Late Effects Guidelines

Exposure Type	Number of COG Late Effect Guidelines Informed by CCSS Publications	Number of CCSS References	
		Version 4.0	Version 5.0
Chemotherapy	15/33 (45%)	8	23
Radiation	31/54 (57%)	47	62
Surgery	8/36 (22%)	3	16
Any Cancer Experience	6/6 (100%)	18	33
Blood/Serum Products	1/3 (33%)	1	1
Cancer Screening Guidelines	3/9 (33%)	5	5
TOTAL	64/141 (45%)	82	140

- 140 total references to CCSS publications
- 45% of **COG Guidelines** informed by CCSS publications
  - Radiation (57% informed by CCSS publications) and Cancer Experience late effects (100%) most impacted

- **International Guideline Harmonization Group** Surveillance Recommendations (**28 total refs.** in 6 manuscripts)
  - Breast Cancer, Lancet Oncology 2013 (3 refs.)
  - Cardiomyopathy, Lancet Oncology 2015 (7 refs)
  - Ovarian Insufficiency, JCO 2016 (6 refs)
  - Male Gonadotoxicty, Lancet Oncology 2017 (6 refs)
  - Ototoxicity, Lancet Oncology 2019 (1 Ref)
  - Thyroid Cancer, Cancer Treatment Revs., 2018 (5 refs.)

Overall Survival after Solid Organ Transplantation

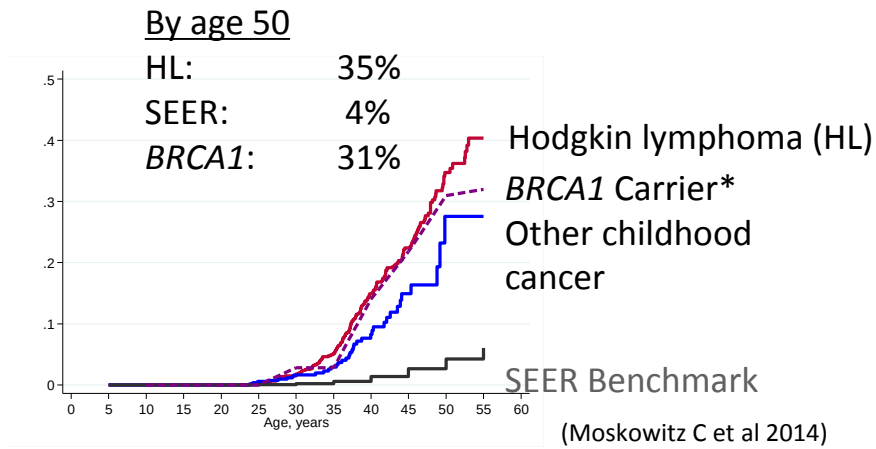


Solid organ transplantation is uncommon.

However, transplantation should be considered for 5-year survivors with severe end-organ kidney and heart failure.

Dietz AC et al, Lancet Oncol, 2019

Breast Cancer Following Treatment for Childhood Cancer



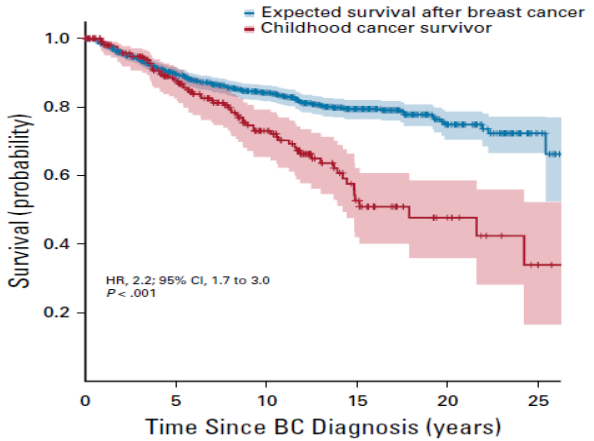
(Moskowitz C et al 2014)

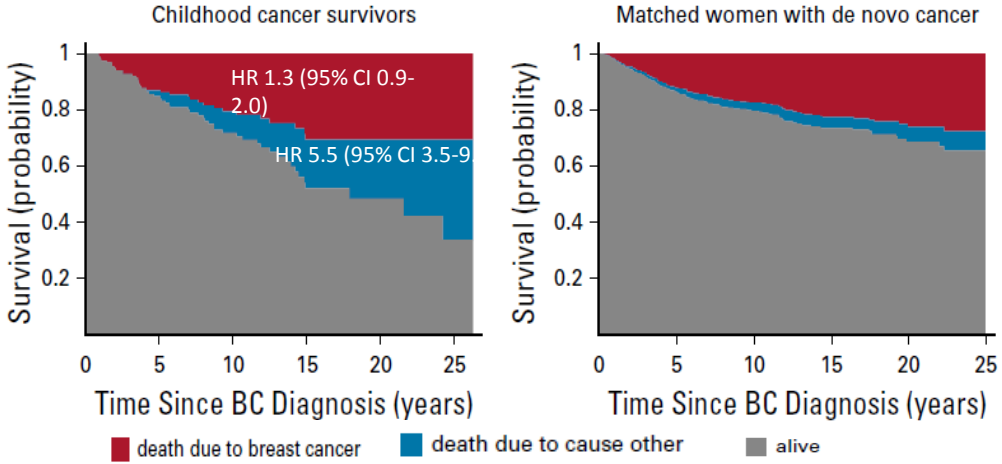
Breast RT Dose	Anthracyclines	
	No	Yes
	OR (95% CI)	OR (95% CI)
0 - <1Gy	1.0	1.0
1 - <10Gy	2.1 (0.9-4.8)	3.7 (1.4-10.3)
10+ Gy	**9.6 (4.4-20.7)**	**19.1 (7.6-48.0)**

- Increased risk similar to BRCA1 carrier (Moskowitz C et al 2014)
- Novel identification of increased risk (4 fold) with anthracycline or alkylator exposure (Henderson TO et al, 2016)
- Anthracycline increases risk with XRT dose-
  - Nested case control 271 women with subsequent breast cancer
  - Odds ratio for breast cancer increased with cumulative anthracycline dose: OR per 100mg/m^2 = 1.23 (95% CI 1.09-1.3) (Veiga LH et al, JAMA Pediatr, 2019)

Survival After Breast Cancer as SMN

- 278 survivors with breast cancer; Compared to matched control (SEER) with de novo breast cancer
- Overall survival at 10 years - Childhood Cancer survivors 73% (65-80%); SEER 88% (82-92%)
- Increased mortality after breast cancer is largely attributable to the burden of comorbidity
- Risk reducing interventions are needed.





Moskowitz CS et al, J Clin Oncol 2019

Anthracycline Dose Equivalence Ratios for Late-Onset Cardiotoxicity

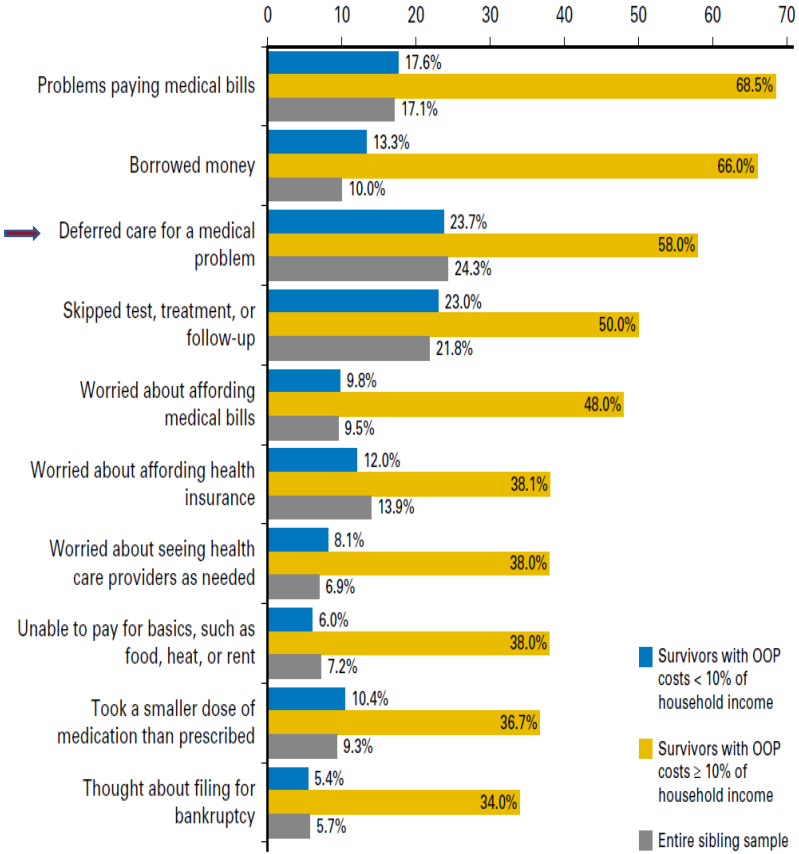
- Assumption: Established risk for anthracycline hematologic toxicity is equivalent to risk for late-onset cardiotoxicity
- International collaboration: >29,000 survivors (CCSS, Dutch LATER, SJLIFE)
- Median follow-up of 20 years; 399 cases of cardiomyopathy

	Dose Ratio	95% CI
Daunorubicin	0.6	(0.4-1.0)
Epirubicin	0.8	(0.5-2.8)
Mitoxantrone	10.5	(6.2-19.1)

Daunorubicin associated with decreased risk for cardiomyopathy compare to Doxorubicin. Mitoxantrone risk for cardiotoxicity has been significantly underestimated.

Feijen et al, JAMA Oncol 2019

Psychosocial & Cognitive Outcomes



- Financial Toxicity: Survivors more likely to have out of pocket costs >10% of income, which is associated with deferred care, skipping treatment follow-up
  J Clin Oncol, 2017
- Increased risk for underinsurance and "job-lock"
  JAMA Intern Med, 2017; JAMA Onc, 2018
- First comprehensive assessment of QOL and psychosocial outcomes two- to three-decades following childhood cancer
  Cancer Epi Bio Prev, 2008
- Neurocognitive impairment in survivors of CNS and certain non-CNS tumors
  JNCI, 2010; Neuropsych, 2009
- ALL Survivors without CNS RT remain at risk for cognitive dysfunction
  Lancet Psych, 2016

Resource for Genetic Investigation

Genome Wide Association Studies

- Genetic variants associated with therapy-related late effects
- 5,739 survivors genotyped
- Collaboration with Division of Cancer Epidemiology and Genetics (Morton/Chanock)
- 22 ongoing analyses

Next-generation Sequencing

- Whole Exome: 5,451 survivors (Morton/Chanock DCEG)
  Priority: genes associated with radiation sensitivity and cancer predisposition
- Whole Genome (30X) + Whole Exome (100X): 2,900 survivors (SJCRH)

>8,000 survivors sequenced and available as a resource during 2020

Ongoing GWAS studies for Non-malignant Outcomes: Response to RFP

Primary Outcome	PI/Institution	Publication Status
Myocardial Infarction	Morrison/Univ. Texas Health Science Center	Analysis Underway
Stroke	Morrison/Univ. Texas Health Science Center Bowers/Univ. Texas Southwestern	Analysis Underway
Diabetes Mellitus	Lupo/Baylor College of Medicine	Analysis Underway; Abstract Submitted to NASLCCC
Cardiomyopathy Simulation Model	Yeh/Boston Children's Hospital, Harvard Medical School	RO1 Funded; Analysis Underway
Tinnitus	Dolan/University of Chicago	Manuscript Submitted
Intestinal Obstruction	Madenci/Boston Children's Hospital	Analysis Complete
Anthracycline Cardiomyopathy	Bhatia/University of Alabama Birmingham	Analysis Underway
iPSC-Cardiomyocyte RNAseq Identified Genes and Cardiomyopathy	Reyes/MD Anderson	Analysis Underway
Genetic Polymorphisms in Cyclophosphamide Exposed Survivors	Rotz/Cleveland Clinic	Analysis Underway
Genetic Susceptibility to Neurocognitive Impairment Secondary to Childhood Cancer Treatment	Scheurer/Baylor College of Medicine	Analysis Underway
Genome-wide Investigation of Dyslipidemia and Hypertension	Pluimakers/ Princess Maxima Centre	Analysis Underway
Genetic Risk Prediction Profiles for Fracture Among Childhood Cancer Survivors	Im/University of Alberta	Manuscript Submitted
Developing a Clinical and Genetic Risk Prediction Model for Diabetes Mellitus among Survivors of Childhood Cancer	Lupo/Baylor College of Medicine	Analysis Underway
Genetic Determinants of Posttraumatic Stress Disorder in Pediatric Cancer Survivors.	Recklitis/Dana Farber Cancer Institute	Analysis Complete
GWAS of Cisplatin Induced and Non-Cisplatin Induced Hearing Loss.	Dolan/University of Chicago	Manuscript Submitted
GWAS of Hypertension in Adult Survivors of Childhood Cancer	Pierzynski/ SJCRH	Analysis Complete
A Genome-Wide Association Study for Frailty in Adult		Analysis Underway

Randomized Controlled Intervention Trials

ECHOS - Doubled rate of echocardiography screening with risk-based counsel

EMPOWER - Improved rate of mammography through brief motivational interview

ASK about skin cancer - Doubled skin cancer screening (physician and self-exam)

EQUAL - Remote delivery of diet and physical activity for obesity

EMPOWER - Smartphone-based activation to improve breast MRI screening

Communicating Health Information & Improving Coordination with Primary Care - Improve diagnosis and treatment of traditional CVRFs

- **mHealth**

Childhood Cancer Survivor Study

An NCI-funded resource

New Opportunities

- Evaluate physiologic/neurocognitive aging and underlying mechanism of accelerated aging in the cohort (and compared to siblings) using in-home direct assessment of a subset of survivors
- Enhance the resource to better facilitate conduct of Health Services research
- Continue to facilitate studies utilizing genomic data from cohort, and expanding capability for data sharing for collaboration with other cohorts
- Promote precision prevention by developing clinical risk prediction tools
- Establish a cloud-based data sharing platform that would make all CCSS data, both clinical and genomic, readily available to all investigators
- Expansion of intervention studies portfolio including using mHealth approaches
- Initiate the CCSS Vanguard Cohort: a process of identification, enrollment and follow-up of survivors diagnosed 2000-2020 who received novel therapies as part of standard therapy or protocols, for future expansion of the CCSS resource

Budget – U24 Childhood Cancer Survivor Study

Year	Direct Costs
23	$2,489,225
24	$2,924,246
25	$2,871,648
26	$2,543,854
27*	$2,582,212
Total	$13,411,185

- Requesting $13,411,185 (direct costs) and $300,000(direct costs) to be used to fund additional data collection to support the development of a plan for future cohort expansion

* Planned award

Plan for Continuation of CCSS

- Request approval to reissue a letter RFA for 5 years of funding at $2.74 million/year for a total of $13.7 million (direct costs)
- Co-sponsorship from DCCPS, DCEG, DCP
- Additional Evaluation Criteria to include:
  - Expand the use of the cohort particularly in new areas such as neurocognitive/physiologic aging, mechanisms of aging, and health services research
  - Develop, implement and test clinical models for precision prevention
  - Facilitate and stimulate research on genomic and clinical data from CCSS
  - Develop plan for investigators to access genomic/clinical data and evaluate ease of access; Develop “fast track” for investigators using CCSS for grant submission
  - Continue to develop and support intervention studies utilizing new approaches
  - Provide a strategic plan and required data collection that would be necessary to assemble a new cohort in the current era of newer therapies

www.cancer.gov

www.cancer.gov/espanol